REMARKS

Amendments to the claims

Minor editorial amendments are made to claims 1 and 7. New claim 14 is added.

New claim 14 finds support in the specification at least at page 8, line 4 to page 10, line 5. New claim 14 is within the presently examined subject matter, in that the therapeutic aims of the "treatment of SCI" are recited.

Rejection over prior art

Claims 5-13 are rejected under 35 USC § 103(a) as being unpatentable over Tobinick '195 in view of Bertini '276. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that the combination of references cited fails to establish *prima facie* obviousness of the claimed invention. In particular, the references do not establish any expectation of success in making the present invention in one of ordinary skill in the art who reads their disclosures.

The Examiner reasons as follows: Tobinick is alleged to teach that antagonists of interleukin-8 are useful in the treatment of spinal cord injury, but Tobinick does not teach the compounds of formula (II) as a particular IL-8 antagonist or the regimen specified by claims 11-13. Thus, the Examiner asserts that Bertini et al teaches that the compound of formula (II) is a IL-8 antagonist (p.14, lines 12-27), useful in the treatment of IL-8 mediated pathologies, when administered intravenously or intramuscularly, as a bolus, at a daily dosage of from 1 to 1500mg (p.16 line 23 to p.17 line 17).

Applicants respectfully submit that the Specification of the instant Application (at page 3 lines 4-24) describes the state of the art at the time the invention was made: "according to the available knowledge the selective inhibition of IL-8 induced chemotaxis **is not a sufficient condition for the protection of tissues from damage from SCI**. In fact the scientific literature identified numerous factors involved in the aetiology of SCI, among which factors CXCL8 [i.e. the IL-8 receptor] does not certainly appear as one of the most important."

For example, Taoka Y et al (in Journal of Neurotrauma 18,533-543, 2001, copy attached) reports that leukocytopenia and inhibition of leukocyte recruitment by administration of an anti-P-selectin monoclonal antibody, an aspecific blocker of leukocytes adhesion, significantly reduced motor distrurbances observed following SCI . That is, Taoka suggests to the skilled artisan that approaches other than inhibition of IL-8-induced chemotaxis would be effective in treating SCI.

The specification also cites Segal J.L et al Arch. Phys. Med. Rehabil.78, 44-47 1997 (copy attached) for the proposition that recent (at the time of filing of the present application) research had also shown elevated plasma levels of inflammatory mediators including IL-1, IL-6, the soluble-IL2-receptor and intercellular adhesion molecule –1 (ICAM-1) in patients with long standing SCI. The specification also describes US2001/0016195 (Tobinick, the primary reference cited by the Examiner) as disclosing "the treatment of a number of different pathologies, including SCI by means of antagonists of IL-1, IL-6 and IL-8". This reference does not correlate SCI with IL-8. In fact at paragraph [0052] Tobinick recites that IL-1 is a proinflammatory cytokine which has been implicated in the inflammatory response occurring, among other sites, also in the spinal cord, but in the same paragraph it is also said that IL-8 and IL-6 are both proinflammatory cytokines, like IL-1. Consequently Tobinick only hypothesizes that IL-8, being a proinflammatory cytokine like IL-1, might be implicated in SCI, but no direct correlation is made between inhibition of IL-8 activity and effective treatment of SCI.

Tobinick provides no experimental evidence supporting a supposition that IL-8 antagonists can be used for the treatment of spinal cord injury. In fact, in the "experimental results" [0061 ff.] presented in the reference, only treatment with a TNF antagonist (Etaneracept™) is disclosed. With respect to their description of treatment of "acute spinal cord injury", only generalized disclosure that a "cytokine antagonist" should be used is made. There is markedly absent any suggestion that antagonism of IL-8 would be effective in treating SCI.

In view of the foregoing, Applicants respectfully submit that one of ordinary skill in the art at the time the invention was made would not have any reasonable expectation of success in using IL-8-induced chemotaxis inhibitors in the treatment of SCI.

Bertini EP '276 does not remedy the above deficiency of Tobinick.

The Examiner cites Bertini for disclosure of the compounds recited in the present claims and for disclosure that such compounds are useful as inhibitors of IL-8-induced chemotaxis of lymphocytes. At [0048] and in claim 9 of Bertini the diseases are listed involving the aforementioned mechanism, namely psoriasis, rheumatoid arthritits, ulcerative cholitis, acute respiratory insifficiencym idiopathic fibrosis, glomerulonephritis. The Examiner might note that spinal cord injury is however **not** mentioned.

It follows that Bertini is unable to overcome the above-stressed deficiency of Tobinick; in other words Bertini is silent about any possible existence of a direct correlation between polymorphonuclear cell chemotaxis induced by IL-8 and spinal cord injuries.

In view of the foregoing Applicants submit that from Tobinick and Bertini et al, the skilled person would not have had any reasonable expectation of success in using the compounds of formula (I), and even more so the specific the compound of formula (II) and (III), in the treatment of SCI. Therefore the invention as claimed in claim 5 is unobvious over the cited references and the instant rejection should be withdrawn.

Furthermore, Applicants assert that the compounds of formula (I) are not only active to reduce leukocyte infiltration but also to block apoptosis of oligodendrocytes. (see page 8 lines 12-25 of the specification). The finding of this latter activity for these compounds is a result that is unexpected by one of ordinary skill in the art who reads Bertini EP '276 and indeed is not at all suggested by Tobinick '195.

Still further, as clearly described at page 8, lines 12-25 of the instant specification, "It is well known that apoptosis of oligodendrocytes is a crucial event during the early stages after traumatic lesion of the spinal cord and that the extent of neurological recovery is also dependent

on how such process can be counteracted or attenuated. Oligodendrocyte death causes demyelination of the axons spared by the lesion, thus causing loss of the ability to conduct the electrical impulse across the lesion site. The pharmacological attenuation of oligodendrocyte apoptosis thus is a primary target of any pharmacological treatment aiming at promoting recovery after SCI."

The present Inventors have demonstrated, surprisingly, that the compounds of formula (I), such as the compound of formula (II) and the compound of formula (III) blocked oligodendrocyte apoptosis determined after SCI by 85% and 65%, respectively (Table 2 at page 9 of the instant specification). Applicants have also demonstrated that the compounds of formula (I) are also effective in reducing the tissue damage following to SCI. In fact as shown in Table 3 at page 10, treatment with the compounds described above significantly reduced the tissue damage at the site of the lesion and the extension of the post traumatic cavity 28 days after SCI (See page 8 line 26- page 9 line 2).

Furthermore, the efficacy upon functional recovery of the compounds of formula (I) was evaluated after s.c. continuous infusion. As shown in Figure 3, treatment with the compound of formula (II) at an infusion rate of 5 mg/kg/h or 10 mg/kg/h significantly promoted functional hind limb recovery after SCI evaluated up to 14 days after SCI . In addition, the compound of formula (II) administered by s.c. infusion at an infusion rate of 10 mg/kg/h significantly promoted functional hind limb recovery even if compound administration started from 24 hours after SCI. As shown in Figure 4 the recovery was progressive, being the most effective in the period between the 7^{th} and the 24^{th} day after SCI (see page 9 lines 3-11 of the Specification).

The above-described excellent results obtained with the compound of the present invention in terms of blocking oligodendrocyte apoptosis, reducing tissue damage and promoting functional recovery could not be expected by one of ordinary skill in the art who reads Tobinick '195 together with Bertini EP '276. Such unexpected results provide objective evidence of

unobviousness of the present invention sufficient to rebut any case of *prima facie* obviousness deemed established by the references.

For all of the above reasons, Applicants submit that the rejection of claims 5-13 as obvious over Tobinick '195 in view of Bertini EP '276 should be withdrawn.

Applicants submit that the present claims are patentable over the prior art of record. The favorable actions of withdrawal of the standing rejection and allowance of the present claims are respectfully requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $130.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Registration No. 36,623, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

Mark J. Nuell
Registration No. 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive, Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant

Attachments: Segal et al.
Taoka et al.